

**The Constitution
of the
Nitro- α -carbopyrrolic Acids**

By
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1915

*Ann Arbor
1915*



The Constitution of the Nitro-*a*-carbopyrrolic Acids

A Dissertation

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By

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I. HISTORICAL PART.

In 1834 Runge¹ observed in coal tar and in bone oil a substance by which a pine chip moistened with hydrochloric acid was turned purple-red. To this substance he gave the name pyrrole. He thought it was a gas. Anderson² in 1857 recognized the crude material with which Runge had experimented as a mixture of pyrrole compounds. From this mixture he isolated pure pyrrole and determined the empirical formula.

In 1846 Malaguti³ obtained by the dry distillation of ammonium mucate a substance of the empirical formula $C_8H_6ON_2$, which he called bipyromucamide. This substance was dibasic in contradistinction to the pyromucic acid obtained by Schwanert⁴ in 1860 by the dry distillation of mucic acid. It occurred to Schwanert that either pyromucic acid was dibasic or that the so-called bipyromucamide described by Malaguti was not a derivative of pyromucic acid. He found the latter to be true. In his attempts to arrive at the constitution of the substance which Malaguti had prepared he was guided by the idea that it, if the amide of a dibasic acid, must be converted by hydrolysis into the ammonium salt of the same, and that the acid corresponding to this salt might perhaps lend itself to decomposition into simpler substances which might possibly be recognized as derivatives of a monobasic pyromucic acid. The result of his investigation, however, showed that Malaguti's bipyromucamide upon hydrolysis yielded ammonia and a new monobasic nitrogen-containing acid constituted similarly to anthranilic acid. To this he gave the name carbopyrrolic acid. The bipyromucamide was renamed carbopyrrolamide. The direct method of preparation of carbopyrrolic acid was as follows: Ammonium mucate was submitted to dry distillation at 300° . The aqueous portion of the distillate contained the carbopyrrolamide, which was separated by crystallization. After boiling with barium hydroxide it yielded a barium salt from which the carbopyrrolic acid was obtained by acidification and extraction with ether. The yield was very small.

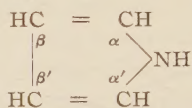
¹ Pogg. Ann. **31**, 65 (1834).

² A. **80**, 63 (1851); A. **105**, 349 (1858).

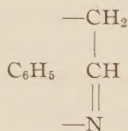
³ Compt. rend. **22**, 856 (1846).

⁴ A. **116**, 265 (1860).

While the empirical formula of carbopyrrolic acid and some of its properties were thus known in 1860, no definite constitution was assigned to it until 1870 when Baeyer¹ suggested the structural formula for pyrrole which is one of the most commonly used at present.



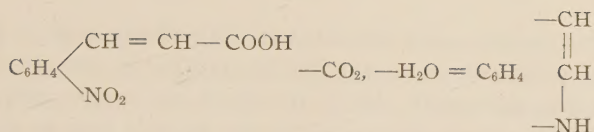
Baeyer was led to adopt this structural formula from the following considerations: The decomposition products of indigo-blue were known to include aniline, anthranilic acid and benzaldehyde. In view of the fact that picric acid and nitrosalicyclic acid are formed by the action of nitric acid upon them, these three substances are divisible into two groups, in the one aniline and benzaldehyde which have a carbon atom or a nitrogen atom joined to the benzene nucleus, and in the other anthranilic acid which contains both a nitrogen atom and a carbon atom joined to the benzene nucleus. From these facts Baeyer and Knop² concluded that indole, the mother substance of indigo, possessed the following formula:



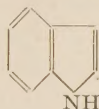
The positions of the linkings in respect to the benzene nucleus were not known to them. This formula best explained the decomposition products of indigo. In every case the second carbon atom to the benzene ring was taken away and, further, in the formation of aniline also the other carbon atom was removed, whereas in the formation of benzaldehyde the nitrogen atom was removed along with the middle carbon atom of the side ring. There was doubt, however, about the distribution of the hydrogen atoms and the method of linking in the side chain. This point was made clear by the synthesis of indole accomplished by distillation of nitrocinnamic acid with potassium hydroxide.

¹ Ber. 3, 514 (1870).

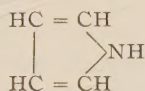
² A. 140, 1 (1866).



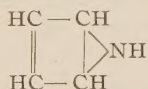
From the work of Victor Meyer it came no longer to be doubted that the so-called meta-derivatives of benzene, among which indole is included, contain the side chain or other substituents joined to the -1,2- positions of the benzene ring. The following structure would then represent indole:



It was known that indole and pyrrole had some common properties; they both react with potassium, and both give the pine chip reaction. Therefore indole was regarded as composed of a benzene ring and a pyrrole ring just as naphthalene consists of two benzene rings. If one erases the six-membered ring of indole, replacing each former bond of attachment to the five-membered ring with a hydrogen symbol, there is left the formula for pyrrole:



In 1877 Schiff¹ presented a new formula for pyrrole



in order to express the relation between it and the compounds of the mucic acid series. This formula, moreover, under the acceptance of the Dewar formula for pyridine would have explained most simply the transition of pyrrole by the action of bromoform to bromo-pyridine, under the assumption that the entering carbon atom of bromoform had taken the para position to the nitrogen atom. After Weidel² had shown that the bromo-pyridine thus formed from pyrrole and bromoform was not a para- but a meta-derivative, and after Ciamician and Silber³

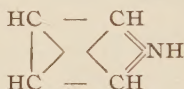
¹ Ber. 10, 1193 (1877).

² M. 6, 664 (1885).

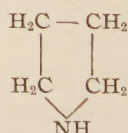
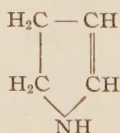
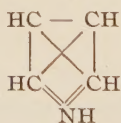
³ Ber. 20, 191 (1887).

had added to the meta-substituted derivatives a meta-phenylpyridine, obtained from pyrrole by means of benzal chloride and sodium alcoholate, there remained no longer any doubt that the fifth carbon atom entered the pyrrole ring in the meta position when the pyridine ring was to be formed. Hereby the Baeyer formula became the more firmly established at the expense of the Schiff formula.

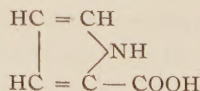
The following formula for pyrrole was proposed by Bamberger¹ in 1891:



He based his argument for this formula upon the observation that the capacity for forming additive compounds is almost entirely lacking for the nitrogen atom of pyrrole and its homologues. Such capacity is expressive of the tendency toward a change of valence characteristic of trivalent nitrogen. These facts indicated to Bamberger that the nitrogen atom in pyrrole existed in quinivalent state. When pyrrole has taken up additional hydrogen atoms, however, it has undergone a fundamental change. Its basic character has greatly increased and the imino group has become possessor of its normal properties. The proposed structural formula accounted for this behavior by representing a decrease of the valence of the nitrogen atom in pyrrole upon the addition of hydrogen atoms to pyrrole.



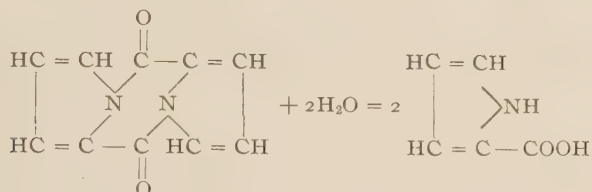
With the presentation of Baeyer's structural formula in 1870 it became possible to assign a definite structure to the carbo-pyrrolic acid of Schwanert, which acid from its preparation from mucic acid was represented as having the carboxyl group in the position adjacent to the nitrogen atom.



Since that time various methods have been found for the prep-

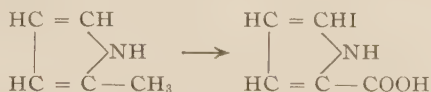
¹ Ber. 24, 1758 (1891).

aration of α -carbopyrrolic acid. In 1880 Weidel and Ciamician¹ obtained by the dry distillation of gelatine a crystalline substance to which the name pyrocoll was given. This substance upon hydrolysis yielded α -carbopyrrolic acid. Upon the basis of this decomposition the following constitution was assigned to pyrocoll:



Pyrocoll was also obtained in 1884 by Ciamician and Silber² by heating α -carbopyrrolic acid with acetic anhydride.

In 1881 α -carbopyrrolic acid was obtained by Ciamician³ by the oxidation of homopyrrole, $\text{C}_4\text{H}_7(\text{CH}_3)\text{N}$, with potassium hydroxide, a method similar to the one used by Barth⁴ to oxidize homologues of phenol.



The potassium homopyrrole was introduced into an excess of molten potassium hydroxide, in which it soon dissolved with a violent evolution of hydrogen. It was found difficult to determine the right moment to stop the reaction. The molten mass was dissolved in water, made slightly acid with very dilute sulphuric acid and the free carbopyrrolic acid removed by extraction with ether.

In 1884 Ciamician and Silber,⁵ following the method used by Senhofer and Brunner in introducing the carboxyl group into phenol, obtained α -carbopyrrolic acid by heating pyrrole and an aqueous solution of ammonium carbonate in a sealed tube. The heating was continued from six to ten hours at a temperature of 130° – 140° . The contents of the tube, which showed slight carbonization, consisted, in addition to ammonium car-

¹ M. **1**, 279 (1880).

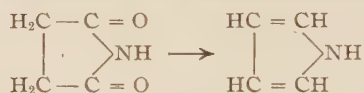
² Ber. **17**, 103 (1884).

³ Ber **14**, 1056 (1881).

⁴ A. **154**, 360 (1870).

⁵ Ber. **17**, 1150 (1884).

bonate, of a small oily layer of unaffected pyrrole and of a bright brown liquid which contained the ammonium salt of the acid sought. The contents were poured into a retort and this was heated until the major portion of the ammonium carbonate and of the pyrrole was driven off. The remaining liquid was concentrated by evaporation and when cold made slightly acid with dilute sulphuric acid. To remove the acid sought from the influence of the sulphuric acid the solution was at once shaken with ether. The ether extract contained the α -carbopyrrolic acid. This was the first method by which α -carbopyrrolic acid could at the time be completely synthesized from pyrrole; pyrrole had been prepared in 1877 by Bell¹ by passing diethylamine through a heated tube, and in 1879 by Bell² by the reduction of succinimide.



In 1884 Ciamician and Silber,³ following the method used by Reimer and Tiemann⁴ of preparing aromatic hydroxy acids from phenols, prepared α -carbopyrrolic acid by the action of carbon tetrachloride upon pyrrole in the presence of potassium hydroxide. Pyrrole, carbon tetrachloride and potassium hydroxide dissolved in alcohol, and after the addition of the necessary amount of water, were placed in a closed flask and heated for twenty-four hours in a steam bath. After the heating the flask contained, in addition to potassium chloride, a brown liquid and a resinous substance. The liquid was concentrated by evaporation and acidified with sulphuric acid and finally extracted with ether. After evaporation of the solvent the residue was dissolved in water, filtered clear of resin and treated with lead acetate. A white precipitate was thus formed from which the free acid was obtained by treatment with hydrogen sulphide and subsequent extraction with ether.



Also in 1884 Ciamician and Silber,⁵ following the well-known method for the conversion of phenols into aromatic hydroxy-

¹ Ber. **10**, 1962 (1877).

² Ber. **13**, 877 (1880).

³ Ber. **17**, 1437 (1884).

⁴ Ber. **9**, 1285 (1876).

⁵ Ber. **17**, 1438 (1884).

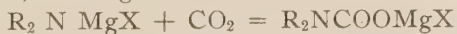
acids, prepared α -carbopyrrolic acid by the action of carbon dioxide upon potassium pyrrole. Potassium pyrrole was heated at a temperature of 200° – 220° , in a stream of carbon dioxide. A portion of the substance distilled off as pyrrole, while another portion was converted into the potassium salt of the acid. The free acid was removed by acidification with dilute sulphuric acid and extraction with ether.

In 1900 Bamberger and Djierdjian¹ obtained α -carbopyrrolic acid by the oxidation of pyrrolaldehyde. This latter substance they prepared by the action of chloroform upon pyrrole in the presence of potassium hydroxide.



The pyrrolaldehyde was dissolved in water and gradually treated with an alkaline solution of potassium permanganate. The solution became green at first and finally brown. The filtrate from the reaction mixture was treated with sodium chloride, freed from the material not acted upon by extraction with ether, acidified in the cold and finally extracted with ether. This latter extract contained the acid.

Of the methods already given only one, namely that in which pyrrole is heated with an aqueous solution of ammonium carbonate, was regarded by Ciamician² as of practical value for the preparation of α -carbopyrrolic acid in any considerable quantity. In 1909 Oddo³ announced a new method, by use of which α -carbopyrrolic acid could be obtained from pyrrole in good yield. He discovered that the imino hydrogen atom of pyrrole would react with the Grignard reagent. This followed naturally from what was already known of the behavior of primary amines⁴ and of secondary amines.⁵ It was also known that the magnesium halide compounds of the secondary amines would absorb carbon dioxide, forming the carbamate.⁶



When the Grignard reaction was carried out with quinoline it was found that the RMgX added to the nitrogen atom,⁷ and

¹ Ber. **33**, 536 (1900).

² Ber. **17**, 1438 (1884).

³ Gazz. **39**, [1] 649 (1909).

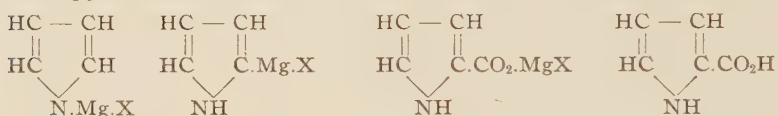
⁴ Bull. soc. chem. **29**, 314 (1903).

⁵ Compt. rend. **138**, 1427.

⁶ Ber. **37**, 3978 (1904).

⁷ Ber. **37**, 3336, 4666, 4673, 4679 (1904).

that when this compound was treated with water the magnesium halide was split off and the radical represented by R attached itself to the alpha carbon atom. Oddo found that the Grignard reagent would form an additive compound with pyrrole in which the magnesium halide was attached to the nitrogen atom. This compound upon treatment with carbon dioxide underwent a shifting of the magnesium halide from the nitrogen atom to the alpha carbon atom, and a subsequent addition of carbon dioxide to form the magnesium halide derivative of the α -carbopyrrolic acid. This substance upon treatment with water yielded α -carbopyrrolic acid.



The first nitro derivative of a pyrrole compound was obtained in 1882 by Weidel and Ciamician.¹ Pyrocoll does not dissolve in ordinary cold nitric acid but when treated with fuming nitric acid it was found to enter into reaction with the evolution of vapors of nitrogen tetroxide, at the same time warming the liquid, and thus destroying the products formed at the beginning of the reaction. To moderate the reaction the pyrocoll was added in small portions to an excess of cold fuming nitric acid, after which the solution was gently warmed upon the water bath until there was no longer an appreciable evolution of nitrogen tetroxide. The mixture was thereupon poured into cold water when there formed a yellow precipitate which constituted the nitro compound. This substance possessed the empirical formula $\text{C}_{10}\text{H}_4(\text{NO}_3)_2\text{N}_2\text{O}_2$, and to it the name dinitropyrocoll was given.

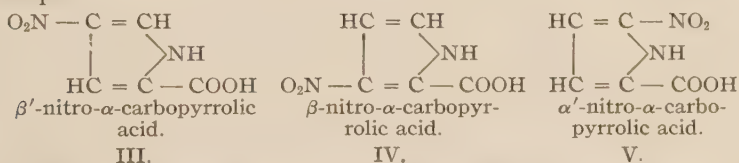
Dinitropyrocoll dissolved readily in cold aqueous alkali, forming a solution of intensely yellow color, which liquid was boiled until it gave no precipitate when acidified. After cooling it was made acid with dilute sulphuric acid, and then extracted with ether. From this ether extract there was obtained a mass of yellow crystals which were purified by recrystallization from water. This new substance was a mononitro- α -carbopyrrolic acid. It crystallized in microscopic needles with one molecule of water of crystallization which completely disappeared when the substance stood *in vacuo* over sulphuric acid. It melted at

¹ Gazz. 12, 39 (1882).

144°–146°, forming a yellow liquid. The aqueous solution gave with lead acetate a yellow precipitate soluble in an excess of the reagent. Ferric chloride produced with it a yellow precipitate. Silver nitrate produced no appreciable reaction. With ammonium hydroxide it gave a yellow salt, the aqueous solution of which formed a voluminous yellow precipitate with silver nitrate. With barium hydroxide it gave a yellow precipitate of the barium salt. This, then, describes the preparation and properties of the first nitrocarbopyrrolic acid. The dinitropyrocoll from which it was obtained must contain the two residues of the nitric acid symmetrically placed in the two pyrrole nuclei, for it was transformed by the action of the alkali into only one nitrocarbopyrrolic acid.

The result above showed that pyrrole derivatives were not destroyed by the action of nitric acid, but easily yielded nitro compounds, therein resembling the well-known behavior of aromatic substances.

The mononitrocarbopyrrolic acid just described is naturally but one of the three isomeric acids which correspond to the three different structures depending upon the position of the nitro group.



In 1886 Ciamician and Silber¹ reported that all attempts to prepare the other two isomeric acids were unsuccessful, for when carbopyrrolic acid was treated directly with nitric acid carbon dioxide was evolved and the two isomeric dinitropyrroles were formed.

In 1889 Anderlini² showed that if the nitration were performed upon the α -carbopyrrolic ester, rather than upon the acid, the splitting off of carbon dioxide could be prevented. The methyl ester was slowly added to a strong nitric acid cooled with ice. The dark brown solution thus poured was at once formed into a large amount of water, this aqueous solution almost neutralized with sodium hydroxide, and finally made slightly alkaline with

¹ Ber. **19**, 1080 (1886).

² Gazz. **19**, 90 (1889).

sodium carbonate solution. By extraction of this weakly alkaline solution with ether there was obtained a mass of bright yellow crystals which recrystallized colorless from hot water. This was the methyl ester of a new mononitro- α -carbopyrrolic acid. By hydrolysis this ester yielded a nitrocarbopyrrolic acid which crystallized from water in the form of pale yellow needles. Like the first acid described it contained one molecule of water of crystallization which disappeared when the substance stood over sulphuric acid. The anhydrous acid melted with decomposition at 217° .

The third isomeric nitrocarbopyrrolic acid predicted from theory was obtained by Anderlini¹ in the same year. The method which he employed was the same as that used in preparing the acid just described. The slightly alkaline solution, from which the ester of the acid above had been removed by extraction with ether, was again made slightly acid and again extracted with ether. After evaporation of the solvent there was left a mass of various nitro compounds, from which it was found possible to separate, by fractional crystallization from water, the methyl ester of the third isomeric acid. This ester upon hydrolysis yielded a product which crystallized from water in the form of pale yellow needles. This acid, like the other two, contained one molecule of water of crystallization. The anhydrous acid melted at 161° .

Anderlini stated that he was unable, for lack of material, to prepare, by the nitration of α -carbopyrrolic ester, the acid melting at 144° – 146° , which Ciamician had obtained by the nitration of pyrocoll. He expressed no doubt that the methyl ester of this acid was among the nitro compounds formed. From the complex reaction products he was able to obtain another crystalline substance which gave the correct analysis for the methyl ester of a dinitrocarbopyrrolic acid.

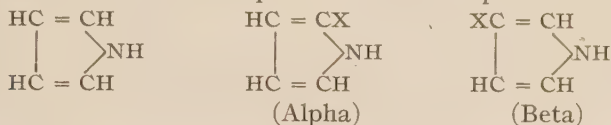
The three mononitro- α -carbopyrrolic acids predicted from theory were thus all known in 1889. They are arranged in the following table:

	Ciamician	Anderlini	Anderlini
		Acids:	
m. p.	144° – 146°	161°	217°
		Methyl esters:	
m. p.		179°	197°

¹ Gazz. 19, 350 (1889).

The position of the nitro group in these three isomeric acids is not determined. The ester of the acid melting at 217° possesses no acid properties, as was evidenced by the fact that it could easily be removed by extraction from an alkaline solution as just described. Anderlini expressed the belief that the acid melting at 217° should be represented with the nitro group in one of the beta positions. He was probably led to this belief by comparing the nitrocarbopyrrolic acids with certain aromatic derivatives in which the acid-conferring influence of negative substituents is strongest when these groups are nearest.

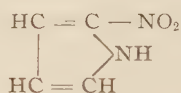
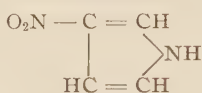
The structural formula for pyrrole admits the theoretical possibility of two isomeric mono-substitution products in which the substituent is in the alpha or in the beta position.



There should be then, theoretically, two isomeric nitropyrroles. One of these was prepared in 1911 by A. Angeli and L. Alesandri,¹ by the nitration of pyrrole with ethyl nitrate in the presence of sodium alcoholate or of metallic sodium. To pyrrole dissolved in ether there was added ethyl nitrate and metallic sodium. The flask containing this mixture was gently heated. At first the reaction proceeded somewhat rapidly, the sodium dissolving with an evolution of hydrogen. A brown salt was deposited. After the sodium had all dissolved ice was added and the mixture extracted with ether and finally treated with bone-black. Together with the sodium salt of nitropyrrole there was formed sodium nitrite. It was found necessary to eliminate this latter substance. To do this silver nitrate was added to the solution, whereupon the silver salt of nitropyrrole and silver nitrite were precipitated. The first is insoluble in water while the latter is somewhat soluble and could be removed by prolonged washing with cold water. To the salt remaining, while still moist, there was added sodium chloride. Silver chloride separated and the sodium salt of the nitro compound dissolved when a little water was added, forming an intensely yellow solution. This was saturated with carbon dioxide and repeatedly extracted with ether. Upon evaporation of the ether there

¹ *Atti dei Lincei* 20, 1, 311 (1911).

was left a yellow oil which presently crystallized. The crystals thus obtained were recrystallized from ligroin. In the state of highest purity they were in the form of straw-colored shining crystals. When crystallized from water the substance appeared in the form of large opaque rhombohedrons, bright yellow in color. The aqueous solution, after the addition of a drop of ammonia, gave with silver nitrate a yellow precipitate which had the appearance of lead chromate. Angeli and Alessandri asserted that the substance prepared by them is expressible by one of the two formulae:



and that the first deserves the preference since in nitrosopyrrole the nitrous acid remnant occupies the beta position.

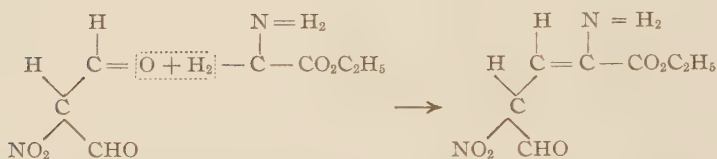
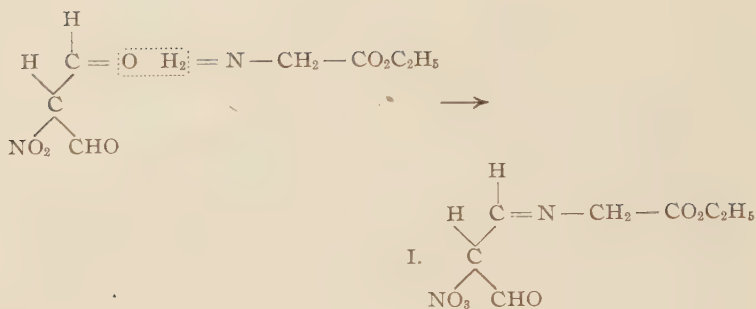
We thus find the literature, which is fairly complete upon the formulae and corresponding properties of pyrrole and pyrrole carboxylic acids, taking cognizance of the existence of three mononitro- α -carbopyrrolic acids and of one nitropyrrole. Experimental evidence to establish the constitution of any of these latter acids is entirely lacking, and only the vaguest hypothesis seems to check the results of the several investigators in this field.

II. THEORETICAL CONSIDERATIONS.

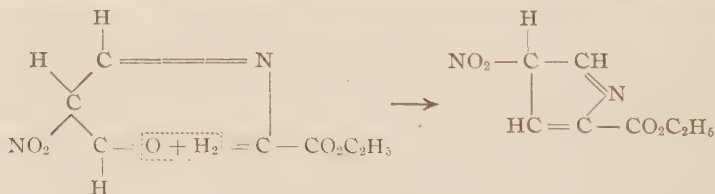
Thus at the beginning of this investigation there were known three isomeric mononitro- α -carbopyrrolic acids, the number predicted upon the basis of Baeyer's structural formula for pyrrole and of the corresponding formula for α -carbopyrrolic acid. From the mode of preparation of these three acids nothing direct could be told concerning the position of the nitro group in the molecule for any of them. It had been observed by Anderlini¹ that the methyl ester of the acid melting at 217° possessed no acid properties, while the methyl ester of the acid melting at 161° , prepared simultaneously with the first, was acid in character. As Ciamician first pointed out, pyrrole has properties similar to those of phenol. The methods used to convert phenols into phenol carboxylic acids are also applicable to the conversion of pyrroles into pyrrole carboxylic acids. The imino hydrogen atom of pyrrole, like the phenolic hydrogen atom of phenol, is replaceable by potassium. It was known that the introduction of nitro groups into the benzene nucleus of phenol considerably increased the acid character of phenol, and of the three mononitro-phenols the ortho compound was the most strongly acid whereas the meta- and para-derivatives were of about equal acidity. Anderlini¹ no doubt reasoning from this knowledge asserted that in the acid melting at 217° the nitro group must be in one of the beta positions, that is in one of the positions farthest from the nitrogen atom. No proof, however, was forthcoming for this assertion.

It was known to us from work performed in this laboratory (as yet unpublished) that when nitromalonic aldehyde and glycine ester, after dissolving in dilute alcoholic solution, were warmed in the presence of a condensing agent, a condensation product was formed which had the empirical formula $C_7H_{10}O_5N_2$. The constitution for it must be represented by one of the following structural formulae:

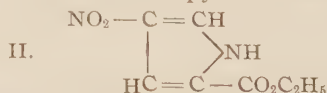
¹ Loc. cit.



Of these the first is correct, for the product gave negative results with the Hofmann carbylamine test for primary amines, negative results with Liebermann's test for secondary amines, and reduced an ammoniacal solution of silver nitrate, showing the presence of an aldehyde group. With this constitution before us, the question arose if the methylene hydrogen atoms also could not be brought into condensation with the remaining aldehydic oxygen atom to form a ring compound of the following structure:



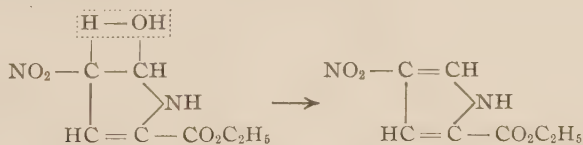
which substance would immediately rearrange itself into the more stable derivative of a carbopyrrolic ester.



We discovered that this could be accomplished under suitable conditions. The beta-aldehydonitroethylidenaminoacetic ester just described, when dissolved in dilute alcohol, and treated with an excess of the condensing agent, readily underwent further condensation, thus forming a new crystalline product which was

found to possess the empirical formula $C_7H_8O_4N_2$. The isolation of the intermediate product was found to be unnecessary so that nitromalonic aldehyde and glycine ester could be transformed at once to the final pyrrole derivative by the use of an excess of the condensing agent.

The manner of this condensation into ring compounds in which the two aldehyde groups of sodium nitromalonic aldehyde become involved is well known and thoroughly established by the work of Hale and others.¹ The isonitro group on the beta carbon atom of the sodium nitromalonic aldehyde immediately upon acidification rearranges itself to some extent into a nitro group and an adjacent hydrogen atom. And when this aldehyde is involved in ring formation this same labile hydrogen atom liberated by acidification immediately transfers itself to some other carbon atom to effect equilibrium and stability of structure. We may thus expect the primary ring structure resulting from the condensation outlined to undergo an addition and an elimination of a molecule of water at one of the unsaturated linkings, and thus itself to be transformed into the more stable pyrrole derivative in the manner here outlined. The end result may be looked upon simply as a transference of a hydrogen atom from the beta carbon atom to the nitrogen atom.



We have consequently no room to doubt the position of the nitro group in the pyrrole ring thus formed. Many examples of similar condensations have been investigated, and in all cases the position of the nitro group remains firmly established upon the beta carbon atom of the nitromalonyl group entering these condensations.

This brings us at once to a final product with the constitution of β' -nitro- α -carbopyrrolic ester, and there remains after the hydrolysis of the same to check if possible the resulting acid with one of the three known nitrocarbopyrrolic acids and thus to establish the constitution of this same acid.

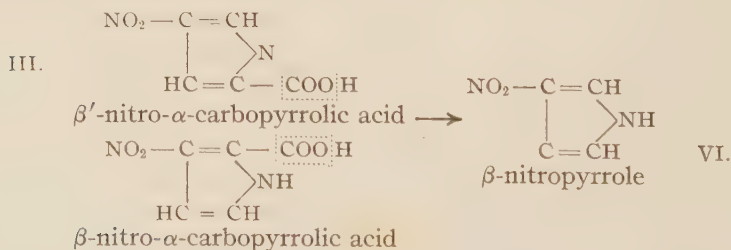
Upon hydrolysis of the ester formed by the condensation

¹ J. Am. Chem. Soc. **34**, 82 (1912).

reaction there resulted β' -nitro- α -carbopyrrolic acid (III), which melted with decomposition at 217° . It was identical in appearance and properties with the acid melting with decomposition at 217° , which was prepared according to the method of Anderlini.¹ This therefore proves that the acid in question, as Anderlini believed, contains the nitro group in one of the positions farthest from the nitrogen atom, namely the β' position.

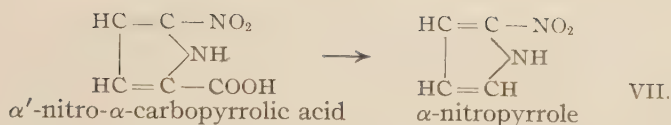
To further establish the identity of the acid obtained from the condensation reaction with the one obtained by Anderlini, nitromalonic aldehyde was brought into condensation with glycine methyl ester. This resulted in a product, β' -nitro- α -carbopyrrolic methyl ester, similar in appearance and properties to the methyl ester of the acid melting at 217° , prepared by the nitration of α -carbopyrrolic ester. Both of these esters as well as their mixture melted at 197° .

Having thus established the structure for one of the three isomeric acids we cast about for some means of establishing that of the other two. It was known that the carbopyrrolic acids upon heating readily gave up carbon dioxide forming pyrrole or its homologues. Our plan of attack was therefore to attempt to expel carbon dioxide from the three isomeric acids and if successful, to base our conclusions in respect to the constitution of them upon a study of the resulting nitropyrroles. That this is theoretically possible from structural considerations is evident from the following figure. The β - and β' -nitro- α -carbopyrrolic acids upon elimination of carbon dioxide should yield only one β -nitropyrrole,



whereas the α' -nitro- α -carbopyrrolic acid should theoretically yield a second isomeric nitropyrrole,

¹ Loc. cit.

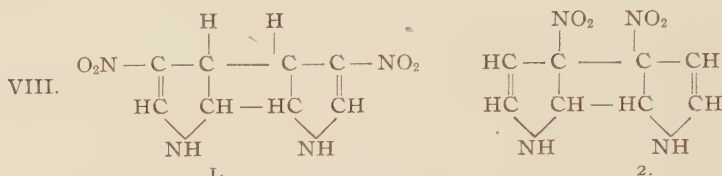


Now it had fallen to us fortunately from the synthesis of our β' -nitro- α -carbopyrrolic acid to have at hand one of the two acids upon which elimination of carbon dioxide must yield the same nitropyrrole. Thus a differentiation between the two acids of unknown constitution could be established from the successful experimentation with them as just outlined. If we had established the formula for the α' -nitro- α -carbopyrrolic acid no such simple transformation as the elimination of carbon dioxide would have sufficed to establish the constitution of the other two acids.

Now a nitropyrrole, presumably a β -derivative (VI), had been prepared as described above by Angeli and Alessandri.¹ They found it to be a crystalline product melting at 63.5° . Guided by the expectation of obtaining this product we made numerous attempts to expel carbon dioxide from the acid already in our possession. The acid was found to decompose violently when heated by itself sufficiently to bring about any change in its properties. When the substance was mixed with naphthalene and the mixture heated in a sealed tube the naphthalene vapors were found somehow to protect the compound and its decomposition products from so violent and complete a decomposition as that observed when the acid was heated by itself. In this manner after heating the mixture to the point of slight charring, we were able to obtain both a small amount of the product melting at 63.5° , and a considerable quantity of a new substance which melted at 101° . This new product possessed the empirical formula, $\text{C}_4\text{H}_4\text{O}_2\text{N}_2$, which is the formula corresponding to a nitropyrrole. It showed a molecular weight, determined from the elevation of the boiling point of a solution in benzene, corresponding to twice the molecular weight indicated by the molecular formula. The substance possessed chemical properties quite comparable to those of the product of the lower melting point. It failed to produce effervescence with sodium carbonate solution. We were driven to the conclusion that the substance was a nitropyrrole, in which the nitro group occupied the beta

¹ Loc. cit.

position, and that it was dimolecular. The following structural formulae would then be possible:



Of these the first deserves the preference. Polymerized pyrrole compounds are known in which the vicinal carbon atoms at one side or the other of the pyrrole nucleus condense, but any product in which the nitro group is attached to the carbon atom or atoms entering into such condensation is unknown. We have therefore one possible structure and no other, and no further possible polymerization to a tripyrrole derivative, such as is well known for free unsubstituted pyrrole, can be expected.

Having thus arrived at a dimolecular β -nitropyrrole, the question arose if it could be converted into the product melting at 63.5° . Our product of the higher melting point showed a molecular weight, determined by the depression of the freezing point of an aqueous solution, corresponding to considerably less than that calculated for the dimolecular substance. This indicated to us that in aqueous solution there was an equilibrium between the two forms, the monomolecular and the dimolecular. From such a cold aqueous solution of the higher melting product we have been able, by repeated crystallization from cold water, to obtain a small amount of the product melting at 63.5° . We have judged from this that the product described by Angeli and Alessandri was monomolecular for it is identical with the substance prepared by us. Although the transformation from the high-melting substance to the low-melting form was accomplished to a small extent only it was sufficient to show that in the nitropyrrole prepared by Angeli and Alessandri the nitro group was, as they thought, in the beta position. We have not been able to prepare their product in sufficient quantity for a molecular-weight determination. As stated above, we were able to prepare a small amount of substance melting at 63.5° by heating β' -nitro- α -carbopyrrolic acid. The substance thus prepared, after having been melted in a tube, was heated for several minutes at 75° - 80° , and then permitted to solidify by

cooling. The melting point was found to have changed to 100° during this treatment. This was found by us to be true with the substance described by Angeli and Alessandri, a fact which apparently escaped their notice. Our attempts to bring about a complete change from the dimolecular form to the monomolecular form in large yield gave negative results. The silver salt of the dimolecular product was treated with sodium chloride and the resulting sodium salt was treated in aqueous solution with carbon dioxide, and extracted with ether. In this manner we obtained a yellow oil similar in appearance to that obtained after a similar procedure according to the method of Angeli and Alessandri. The crystals which separated from this oil, however, melted at 100° . The dimolecular product remained unchanged after having been heated for several hours in the presence of water. We have concluded that the dimolecular structure is by far the more stable.

Having thus established the relationship between the β' -nitro- α -carbopyrrolic acid and the corresponding nitropyrrole, our next attempt was naturally to decompose the two remaining acids to discover which would possibly yield a product like that obtained from the acid already described, and which would possibly yield a new nitropyrrole. We choose to experiment first with the acid melting at 144° – 146° (IV), prepared according to the method of Ciamician by the nitration of pyrocoll. However, when proceeding in the nitration of pyrocoll, the observation was at once made that a mixture of nitro compounds was present, a result which had hitherto escaped the notice of Ciamician. From this mixture we were able to separate not only the acid melting at 144° – 146° , but also the other two isomeric acids, namely those melting at 161° and 217° . Further study of the nitration reaction resulted in establishing the conditions under which the different acids could be obtained respectively in the greatest quantities. This discovery was fortunate, for the preparation of the acid melting at 161° by the nitration of α -carbopyrrolic ester would have been both difficult and prohibitively expensive.

After heating the acid melting at 144° – 146° , mixed with naphthalene we were able to obtain a product identical with that obtained (in this same manner), from β' -nitro- α -carbopyrrolic

acid. We have taken this result as proving beyond a doubt that the acid melting at 144° – 146° is β -nitro- α -carbopyrrolic acid.

The third acid, namely the one melting at 161° must therefore be the α' -nitro- α -carbopyrrolic acid (V). We next began to experiment in it the hope of obtaining a new nitropyrrole predicted from theory, and thus further to establish the validity of our results. This acid was found to decompose more readily than the other two. When heated with naphthalene in a sealed tube at a temperature slightly above its melting point, no change in the contents of the tube could be observed. After heating at higher temperatures, notably 230° – 240° , we found a small quantity of unchanged acid and a considerable quantity of carbon, but no intermediate product. The effect of prolonged heat on this acid in a sealed tube at a temperature not much above the melting point finally yielded a small portion of an intermediate product—namely a nitropyrrole (VII). This nitropyrrole was of a yellow color and refused to crystallize. It was a heavy, oily substance with a characteristic smell. As only small quantities of it could be prepared, insufficient for analysis, further work will be required to establish its composition. There can be no doubt that it is the α -nitropyrrole that we anticipated. The instability of this class of compounds, namely α -nitro-substituted pyrroles is to be related at once to the instability of the compound in question and of derivatives of this same class but of similarly constituted rings. The α -nitro-thiophene and α -nitro-furfurane are not known and hence may be as unstable as is this α -nitropyrrole.

For the purpose to which we have used β -nitro pyrrole, to establish the constitution of the nitro-carbopyrrolic acids, it is unnecessary that this α -nitro-pyrrole be isolated as such. The fact that the constitution of β -nitropyrrole is clearly established, and that the two acids which yield this β -nitropyrrole reveal at once their respective constitutions, leaves us the third possibility, namely, that constitution which must correspond with the α -nitropyrrole whether it be known as such or not.

III. EXPERIMENTAL PART.

The nitromalonic aldehyde used in this work was prepared according to the method of Hill and Torrey,¹ namely that of oxidizing furfural by bromine into mucobromic acid, which was in turn converted into sodium nitromalonic aldehyde by the action of sodium nitrite. The glycine ester was obtained by Fischer's method of hydrolysis of gelatine and treatment of the ester thus formed with alcoholic hydrogen chloride.

β-Aldehydonitro-ethylidenaminoacetic ethyl ester, $C_7H_{10}O_5N_2$ (I).

Equimolecular quantities of sodium nitromalonic aldehyde 1.6 grams, and of glycine ethyl ester hydrochloride 1.4 grams, were dissolved in 6–7 cc. of 60–70 per cent. alcohol. A few drops of piperidine, or of 20 per cent. sodium hydroxide solution, were added, whereupon a red color appeared. The reaction mixture was warmed upon the water bath for a few moments. After 15–30 minutes a yellow crystalline deposit formed. This deposit was removed by filtration, washed with diluted alcohol, and dried upon a porous plate. Yield of the crude product was 80 per cent. of the theoretical. It was purified by repeated crystallization from alcohol. It is readily soluble in acetone, chloroform, ethyl acetate, or acetic acid; fairly soluble in alcohol ether, water, or benzene, crystallizing well from each; slightly soluble in carbon disulphide or carbon tetrachloride, and insoluble in ligroin. It crystallizes best from alcohol or water, appearing in thin light yellow prisms melting at 104° .

ANALYSIS.

0.1702 gram of substance gave 0.2582 gram CO_2 and 0.0791 gram H_2O .

0.1452 gram substance gave 18.6 cc. of moist nitrogen at 24° and 745.4 mm. pressure.

Calculated for $C_7H_{10}O_5N_2$.		Found.
C	41.57	41.37
H	4.98	5.19
N	13.86	14.01

β'-Nitro-α-carbopyrrolic ethyl ester, $C_7H_8O_4N_2$ (II).

¹ Amer. Chem. J. 22, 25 (1899).

Equimolecular quantities of sodium nitromalonic aldehyde, and of glycine ethyl ester 1.6 grams, and 1.4 grams, respectively, were dissolved in 6-7 cc. of warm 65 per cent. alcohol. To this solution were added 2 cc. of 20 per cent. sodium hydroxide solution, whereupon a red color appeared. The reaction mixture was warmed for a moment on the steam bath and then set in a region where the temperature was constant at 50°. When the temperature was permitted to rise above this point a tarry mass formed from which no product could be separated. After 20-30 minutes there appeared dark red crystals which soon spread throughout the solution. The liquid was filtered from the crystals, which were washed with dilute alcohol and dried on a porous plate. The yield of the crude product was about 75 per cent. of the theoretical. β' -Nitro- α -carbopyrrolic ethyl ester crystallizes well from hot water or hot alcohol in colorless glistening prisms. It is readily soluble in acetone or acetic acid; fairly soluble in alcohol, ether, benzene, chloroform, or ethyl acetate; slightly soluble in water, carbon tetrachloride, or carbon disulphide, and insoluble in ligroin. When purified by crystallization from alcohol it was found to melt at 174°. An excess of piperidine was also successfully used as the condensing agent.

β' -Nitro- α -carbopyrrolic ethyl ester was also prepared by the condensation of β -aldehydonitroethylidenaminoacetic ethyl ester. 0.5 gram of this substance, dissolved in 4 cc. of 65 per cent. alcohol, was treated with 20 drops of 20 per cent. sodium hydroxide solution. A red color appeared. The solution was warmed for a moment on the steam bath and then placed upon a water bath kept at about 50°. In 20 minutes a crystalline mass formed. The crystals thus obtained were identical with those already described.

ANALYSIS.

0.1736 gram of substance gave 0.2896 gram of CO₂ and 0.0702 gram of H₂O.

0.1823 gram of substance gave 25.3 cc. of moist nitrogen at 23.2° and 748.2 mm. pressure.

	Calculated for C ₇ H ₈ O ₄ N ₂ .	Found.
C	45.63	45.50
H	4.38	4.52
N	15.22	15.31

β' -Nitro- α -carbopyrrolic acid, $C_5H_4O_2N_2$ (III).

One gram of β' -nitro- α -carbopyrrolic ethyl ester was treated with 15 cc. of 20 per cent. potassium hydroxide solution. The substance readily dissolved with the evolution of heat forming a solution of intensely yellow color. This solution was heated upon the steam bath for 5–6 hours with the occasional addition of a little water. The solution was then surrounded with a freezing mixture and neutralized with concentrated hydrochloric acid, whereupon the yellow color disappeared. The solution was then extracted with ether, from which a pale yellow residue was obtained by evaporation. This residue was recrystallized from hot water. The yield was 90 per cent. of the theoretical. β' -Nitro- α -carbopyrrolic acid is readily soluble in alcohol, ether, ethyl acetate, or acetone; fairly soluble in water or glacial acetic acid; slightly soluble in chloroform, benzene, carbon disulphide, or carbon tetrachloride, and insoluble in ligroin. It crystallizes well from hot water in beautiful, colorless, slender needles, which melt with decomposition at 217° . It crystallizes unchanged from glacial acetic acid.

This acid was also prepared by the hydrolysis of β' -nitro- α -carbopyrrolic methyl ester in the same manner. β' -Nitro- α -carbopyrrolic acid was also prepared according to the method of Anderlini¹ by the nitration of α -carbopyrrolic methyl ester. 0.5 gram of the pure ester prepared by the method of Oddo was added in very small portions to 15 grams of strong nitric acid, 1.50 sp. gr., which was kept at a temperature of -10° . As soon as the substance came in contact with the liquid a red color appeared. This disappeared when the flask was shaken. When all of the ester had been added, the liquid, which had become somewhat darker in color, was poured into about 150 cc. of ice-cold water. This aqueous solution was almost neutralized by the addition of 20 per cent. sodium hydroxide solution, and finally made faintly alkaline with sodium carbonate solution. The alkaline solution was then extracted with ether. Upon evaporation of the solvent a deposit of yellow material was formed. This substance melted at 190° . It was repeatedly recrystallized from hot water and finally appeared in the form of colorless prisms melting at 197° . The yield was less than 10 per cent. of the theoretical. The ester obtained in this manner was dis-

¹ Gazz. 19, 90 (1889).

solved in a few cc. of 20 per cent. sodium hydroxide solution and heated for two hours on the steam bath. The bright yellow solution was then cooled and acidified in the cold with concentrated hydrochloric acid, and finally extracted with ether. The ether extract yielded a small amount of yellow crystals. These were recrystallized from hot water when they appeared in the form of pale yellow transparent needles. They melted with blackening at 216° . When mixed with the product obtained as described above they melted at 216° .

ANALYSIS.

0.2106 gram of substance gave 0.2974 gram of CO_2 and 0.0495 gram of H_2O .

0.1341 gram of substance gave 21.9 cc. of moist nitrogen at 21° and 745.5 mm. pressure.

	Calculated for $\text{C}_5\text{H}_4\text{O}_4\text{N}_2$.	Found.
C	38.47	38.52
H	2.56	2.61
N	17.96	18.05

DETERMINATION OF WATER ON CRYSTALLIZATION.

0.5033 gram of substance lost 0.0508 gram after standing over sulphuric acid for 48 hours.

Loss calculated for one molecule H_2O .	Found.
10.33	10.09

The silver salt was prepared by adding silver nitrate solution to an aqueous solution of the ammonium salt. It formed a yellow, gelatinous precipitate which dried in a red desiccator forming an amorphous, yellow powder.

ANALYSIS OF SILVER SALT.

0.2885 gram of substance gave 0.2064 gram of AgBr .

	Calculated for $\text{C}_5\text{H}_3\text{O}_4\text{N}_2\text{Ag}$.	Found.
Ag	41.04	41.09

The potassium salt was prepared by neutralizing an aqueous solution of the acid with potassium carbonate solution and evaporating the resulting solution. The salt crystallized in lemon-yellow prisms or in needles. The potassium salt puffed up when heated in the flame.

0.1814 gram of substance gave 0.0827 gram of K_2SO_4 .

	Calculated for $C_5H_3O_4N_2K$.	Found.
K	20.17	20.47

β' -Nitro- α -carbopyrrolic methyl ester, $C_6H_6O_4N_2$.

Equimolecular quantities of sodium nitromalonic aldehyde and glycine methyl ester hydrochloride 1.4 grams and 1.0 gram, respectively, were dissolved in 6–7 cc. of warm 65 per cent. alcohol. 2 cc. of 20 per cent. sodium hydroxide solution were added. A red color appeared. The solution was warmed upon the steam bath and then set aside in a warm place. In about half an hour a yellow crystalline substance precipitated. This substance was filtered at the pump, the crystals were washed with dilute alcohol and dried on a porous plate. The yield of the crude product was about 75 per cent. of the theoretical. β' -Nitro- α -carbopyrrolic methyl ester is readily soluble in acetone; fairly soluble in alcohol, ether, benzene, ethyl acetate, chloroform, or acetic acid, crystallizing from each, but best from alcohol; slightly soluble in water, carbon disulphide, or carbon tetrachloride, and is insoluble in ligroin. It crystallizes in the form of colorless prisms which melt at 198° . This substance when mixed with the methyl ester of the nitro acid prepared as already described, by the nitration of the ester of α -carbopyrrolic acid, melted at 198° .

β -Nitropyrrole, $C_4H_4O_2N_2$ (VI).

This compound was prepared according to the method of Angeli and Alessandri.¹ 5 grams of pyrrole were dissolved in 30–40 cc. of dry ether and to this solution there were added 2.4 grams of sodium wire and 9.51 grams of ethyl nitrate. A reflux condenser was connected to the flask which was placed on a water bath kept at about 30° . The upper end of the condenser was closed by a U-tube containing a little strong potash solution. The sodium dissolved slowly with the evolution of hydrogen, while the contents of the flask became dark in color. A dark brown salt settled at the bottom. After 36–48 hours the sodium had all dissolved. To the contents of the flask which were very dark in color small pieces of ice were added, and the mixture extracted several times with ether to remove any pyrrole not acted upon. The aqueous solution was then treated with bone-black. In the absence of all but a ruby light the

¹ Loc. cit.

aqueous solution was treated with silver nitrate solution, whereupon a yellow or brown non-crystalline deposit formed. This deposit was filtered at the pump, and the residue left on the filter was washed repeatedly with cold water, until the washings gave no test for silver or for nitrite. The residue was then, while still moist, treated with dry sodium chloride and the mixture finally shaken about with a little water. Silver chloride was precipitated and the water solution became intensely yellow. After filtering the solution was saturated with carbon dioxide and extracted with ether. The ether extract yielded upon evaporation a yellow oil from which crystals separated after a short time. The quantity of these was very small. When removed and dried on a porous plate they became colorless. They failed to melt below 240° . The yellow oil was dissolved in a mixture of benzene and high-boiling ligroin. This solution was treated with animal charcoal. After the solvent had evaporated there was left a yellow oil from which there appeared, after standing for an hour or more, a few highly refractive crystals. After the oil had stood in the ice chest in a desiccator for several days the yield of these crystals was considerably increased. They melted at 63.5° and after heating in a tube for 10–15 minutes at 70 – 80° the melting point was found to be 100° . A few crystals melting with decomposition at 168° were also obtained from this yellow oil after 10° cooling.

Sym.-Dinitrodipyrrole, $C_8H_8O_4N_4$ (VIII).

Various attempts were made to expel carbon dioxide from β' -nitro- α -carbopyrrolic acid before we found a method which gave satisfactory yields of the derivative sought. The pure acid was mixed with a small amount of powdered pumice and quicklime, and this mixture was heated in a flask immersed in a metal bath. The temperature was gradually raised to 400° . The mixture sintered together and a few colorless crystals collected at the end of the delivery tube. These crystals had no definite melting point, but sublimed when heated. They were apparently an ammonium salt. The contents of the flask smelled strongly of ammonia and of pyrrole. Extraction of the residue with ether failed to give any product. The residue was dissolved in water and the aqueous solution saturated with carbon dioxide and again extracted with ether, but with no result. This same experiment was performed with the variation that the distilling

flask and its contents were suddenly introduced into the metal bath when the latter had attained a temperature of 220° . An ammonium salt was obtained as in the previous case and extraction of the contents of the flask with ether gave no result.

The acid was mixed with soda-lime and distilled in a flask immersed in a metal bath at temperatures from 220° – 400° . A small amount of water condensed in the delivery tube. This smelled strongly of pyrrole and upon evaporation left a brown oily film upon the evaporating dish. The contents of the flask smelled strongly of pyrrol and yielded only an oily film upon extraction with ether.

The acid was heated by itself in a flask immersed in a metal bath at 220° – 230° . The substance melted, blackened, and partly sublimed. The sublimed substance melted at 217° . The contents of the flask gave no product save the original acid when extracted with ether. When the heating was carried on at higher temperatures the blackened substance suddenly and violently decomposed with the formation of a yellow smoke smelling of pyrrole, ammonia, and hydrocyanic acid.

The acid was placed in a bomb tube with a small quantity of water, the tube sealed and heated in a bomb furnace until a temperature of 250° had been reached. The solution became brown and when cold a crystalline deposit formed. Upon opening the tube pressure was observed and gas escaped. The substance in the tube melted not sharply at about 110° . By repeated fractional crystallization there was obtained a small amount of a crystalline product melting at 98° .

0.5 gram of the pure acid was placed in a sealed tube by itself and heated at 230° for 15 minutes. The mass charred, and as the tube cooled a brown, oily liquid condensed upon the walls. This liquid crystallized when the tube became cold. The contents of the tube upon extraction with ether yielded a small amount of product melting at 96° .

0.5 gram of the acid was sealed in a bomb tube and heated in the furnace at 225° for an hour. The mass blackened. When cold the contents were extracted with ether. The ether extract left after evaporation a greenish yellow oil from which small crystals formed. These melted at 63° . The yield was very small, barely enough for a melting point determination. Further attempts to obtain the same product failed.

Experiments were performed using various substances which, it was hoped, would act catalytically in the elimination of carbon dioxide. Powdered pumice, powdered copper, finely divided nickel, and sand were each mixed with the pure acid before heating in a sealed tube. In every case there resulted almost entirely either the unchanged acid or a product melting between 95° and 100° . When the metals were used there was found to be present a small quantity of a brown, amorphous substance which did not melt below 230° .

0.5 gram of the pure dry acid was placed in a 60 cc. distilling flask connected to a suction pump. The flask was placed in a metal bath and gradually heated to 300° at a pressure of 24–26 mm., while a small current of air passed was through the flask. The mass in the flask melted at 217° , became dark in color and foamed slightly. At 225° a white smoke began to pass over into the receiving flask and to settle on the walls. This was the only change noticeable. The product which distilled over, about 0.1 gram, was soluble in ether and in hot water. When recrystallized from water it melted at 97° .

0.5 gram of the pure acid was mixed with 5 grams of naphthalene and heated in a sealed tube for an hour at a temperature of 295° . The contents of the tube became very dark. Upon cooling and after extraction with water no residue was left. 0.5 gram of the acid was mixed with 5 grams of naphthalene and heated in a sealed tube at 260° for two hours. The mass charred. When cold the tube was extracted with water which then formed a yellow solution. This when evaporated left a hard, glassy scale which refused to melt when heated as high as 230° .

One gram of the pure, dry acid was mixed with an equal weight of naphthalene and the mixture heated in a sealed tube while the temperature was raised gradually. The tube was inspected from time to time. At 240° the molten contents began to char. The heating was suspended, the tube removed and cooled. Considerable pressure was observed when the tube was opened. The mass was extracted with ether, the ether evaporated, and the resulting mass was treated with hot water to separate the product sought from naphthalene. The water solution was yellow-brown in color. Upon evaporation of the water on the steam bath a brown mass of crystalline substances was formed. This had no definite melting point but was easily melted when

placed on the steam bath. A portion of it was treated with cold water and upon evaporation of the water, at first upon the steam bath and finally by spontaneous evaporation, a substance was obtained which became waxy at 60° – 63° . This substance was treated with carbon tetrachloride, from which solvent a residue was obtained which melted at 88° . The part insoluble in carbon tetrachloride melted at 65° – 67° . The main part of the mass obtained from the tube was thereupon treated with ice water. The yellow solution thus obtained was evaporated, the residue thus obtained again treated with ice water, and this yellow solution allowed to evaporate spontaneously. There was thus obtained a deposit of yellow crystals melting at 63° – 64° . The yield was less than 0.1 gram. These crystals after standing in a desiccator over night were found to melt at 104° . From this higher-melting product we obtained a small amount of the lower melting product by treatment with ice water as described above. The product melting at 63° was melted in a tube and the heating carried up to a temperature of 80° , after which the tube was removed and cooled. The substance was then found to melt at 107° . Attempts to repeat this preparation have been without success.

1 gram of the pure, dry acid was mixed with 1 gram of naphthalene and the mixture heated in a sealed tube. When the contents began to char the tube was removed, cooled, and extracted with hot water. This aqueous solution left a brown deposit when evaporated just as described in the previous experiment. An extract of this with ice water left a product melting at 96° . This, as well as the product melting at 97° , which had been formed by the vacuum distillation of the acid, was purified by repeated crystallization from water. In this manner there was obtained a product which in the purest condition melted at 101° , forming a yellow liquid. The yield of the product from the acid heated in the sealed tube was about 50 per cent. The substance crystallizes from benzene in pale yellow plates, and from water in pale yellow, transparent prisms. It is readily soluble in alcohol, acetone, ethyl acetate, or acetic acid; fairly soluble in water, benzene or chloroform; almost insoluble in high-boiling ligroin, carbon tetrachloride, or carbon disulphide, and insoluble in low-boiling ligroin.

The product melting at 101° was also obtained by heating the

acid melting at 144° – 146° . 0.4 gram of the pure acid was placed in a sealed tube by itself. This was heated slowly and inspected every few minutes. At 220° the molten contents began to appear darker and to adhere to the walls of the tube, while bubbles formed on the surface of the liquid. The tube was removed and cooled. Considerable pressure was noticeable when the tube was opened. The contents were extracted with water, from which by evaporation a brown oil or sirupy liquid was obtained. This soon crystallized. The crystalline mass was dissolved in ether from which solvent a yellow oil was obtained. After standing for some hours in a desiccator crystals melting at 144° were obtained from this oil. These were removed and the oil was then dissolved in benzene, treated with bone-black and permitted to evaporate. Crystals melting at 94° formed. These after standing in a desiccator over night melted at 117° . They were recrystallized three times with dry benzene, after which they were found to melt at 100° . When mixed with the substance melting at 101° derived from the acid melting at 217° they were found to melt at 100° . The yield was about 0.05 gram.

ANALYSIS.

0.1437 gram of substance gave 0.2273 gram of CO_2 and 0.0493 gram of H_2O .

0.1216 gram of substance gave 26.8 cc. of moist nitrogen at 21.1° and 743.0 mm. pressure.

Calculated for $\text{C}_4\text{H}_4\text{O}_2\text{N}_2$.		Found.
C	42.85	43.05
H	3.56	3.72
N	25.01	25.11

Substance, 0.1294, 0.2694, 0.4222; benzene, 15.2; elevation, 0.097, 0.200, 0.401.

Calculated for $(\text{C}_4\text{H}_4\text{O}_2\text{N}_2)_2$.	Found.
224.06	222.0

Substance, 0.981; water, 32.3167; depression, 0.035

Calculated for $(\text{C}_4\text{H}_4\text{O}_2\text{N}_2)_2$.	Found.
224.06	161.3

The three isomeric nitro-carbopyrrolic acids were all prepared by the nitration of pyrocoll according to the method of Ciamician,¹ or by modifications of this method.

¹ Loc. cit.

β -Nitro- α -carbopyrrolic acid (IV).

2 grams of pyrocoll were added in small portions to about 40 grams of fuming nitric acid, at a temperature of 4° – 10° . The pyrocoll dissolved readily and quietly, provided the portions added were not too large, and the brown fumes of nitrogen tetroxide were given off in considerable quantity. When the substance had all been added, the liquid, dark brown in color, was gently heated on the steam bath until the evolution of the vapors of nitrogen tetroxide had almost ceased. The liquid was then poured into an excess of cold water, whereupon a yellow-brown, non-crystalline precipitate formed. This was filtered at the pump and treated with 20 cc. of 20 per cent. sodium hydroxide solution. The nitrated pyrocoll dissolved in the alkali forming an intensely yellow solution. This was heated on the steam bath until a test portion failed to give a precipitate when acidified with dilute sulphuric acid. The solution was then cooled and acidified in the cold with dilute sulphuric acid. When completely acidified the yellow color disappeared to a great extent. The solution was then extracted with ether from which extract a mass of yellow crystals were obtained by evaporation. This mass was dissolved in hot water, treated with bone-black and allowed to crystallize. There formed from this solution small masses of microscopic yellow crystals, and as the water evaporated fine, yellow needles gathered at the lower portions of these masses. The two products were removed and dried. The two kinds of crystals were separated with the aid of a knife blade and their melting points were observed. The crystals first formed melted at 140° – 143° . When recrystallized from water they were found to melt at 145° . The yield of the first product was 40 per cent. of the theoretical, while that of the other product was very small. This other product melted at 216° , blackening as it melted. Upon recrystallization from water the substance appeared in the form of pale yellow needles melting with decomposition at 217° , which needles when mixed with the pure acid, obtained from the condensation of nitromalonic aldehyde and glycine ester, melted at 217° with decomposition. It thus appeared that at least two of the isomeric acids were formed by the nitration of pyrocoll.

β -Nitro- α -carbopyrrolic methyl ester.

This substance was prepared by heating the silver salt of β -nitro- α -carbopyrrolic acid with methyl iodide in a closed flask at the temperature of the steam bath. After heating for an hour the flask was cooled and the contents extracted with ether, from which solvent a yellow crystalline substance was obtained. This when purified by recrystallization from alcohol appeared in colorless needles melting about 160° . They are readily soluble in acetone; fairly soluble in ether, benzene, ethyl acetate, chloroform, or acetic acid; slightly soluble in water, carbon disulphide, or carbon tetrachloride; and insoluble in ligroin.

 α' -Nitro- α -carbopyrrolic acid, $C_5H_5O_4N_2$ (V).

A substance melting above 150° had been observed to be formed on the sides of the crystallizing dish when we were carrying out the nitration as just described. This substance was found upon purification to melt at 160° . In the hope of getting a better yield of this product, which we thought to be the acid described by Anderlini, various experiments were carried out, and we have found the following to be the most satisfactory: 2 grams of pyrocoll were added in small portions to an excess, 40 grams, of strong nitric acid (1.50 sp. gr.), at a temperature of -4° to -10° . The pyrocoll dissolved readily, forming a dark brown solution, and the brown fumes of nitrogen tetroxide appeared. After the substance had been added the solution was gently warmed on the steam bath for a few minutes, and then poured into an excess of cold water, whereupon the nitrated product precipitated. This yellow precipitate was somewhat more voluminous than the one obtained by the nitration at higher temperatures. This precipitate was filtered at the pump, and dissolved in 20 cc. of 20 per cent. sodium hydroxide solution. This solution was heated upon the water bath until a test portion gave no precipitate when acidified with dilute sulphuric acid. The solution was then acidified in the cold with dilute sulphuric acid, and extracted with ether. From this extract there was recovered a dark-colored mass which was purified by dissolving in water and treating with bone-black. In this way we were able to obtain a substance which crystallized in clusters of fine, yellow needles. Yield, 35 per cent. of the theoretical. The substance was prepared contained water of crystallization, which completely disappeared when the substance

had stood *in vacuo* over sulphuric acid over night. The water-free acid melted sharply at 161° . This acid is readily soluble in acetic acid, acetone, alcohol, ether, or ethyl acetate; fairly soluble in chloroform, benzene, or water, crystallizing from either when pure in small, colorless needle clusters; slightly soluble in carbon disulphide or carbon tetrachloride, and insoluble in ligroin. It is purified best by recrystallizing in H_2O in which it is somewhat more soluble in the cold than the acid melting at 217° .

From the mother liquor from which the crystals just described had been first obtained, pale yellow, transparent needles formed upon further evaporation. These when purified melted at 217° , blackening the tube. The yield of these was very small—less than 5 per cent.

It was found necessary to work within the temperature limits above. If the acid is warmer than -4° the final product is almost entirely the acid of the lowest melting point, whereas if the nitric acid is colder than -10° the pyrocoll merely dissolves without forming the nitro derivative. When this was the case the precipitate formed by pouring the nitric acid solution into cold water was dark brown in color and yielded, upon hydrolysis and extraction with ether, a black mass smelling of pyrrole and responding to the pine chip test. From this black mass it was impossible to separate any of the three isomeric acids.

α' -Nitro- α -carbopyrrolic acid was also prepared by the nitration of the methyl ester of α -carbopyrrolic acid by the method of Anderlini: After nitration of the ester, the faintly alkaline solution, from which the ester of β' -nitro- α -carbopyrrolic acid had been removed by ether extraction as described above, was again acidified with nitric acid and again extracted with ether. This extract yielded a mass of yellow nitro derivatives from which there were obtained, by fractional crystallization, pale yellow needles, melting at 178° . These were dissolved in alcoholic alkali and heated upon the steam bath. After cooling, the yellow solution was acidified and extracted with ether. From this extract pale yellow needles crystallized. They were recrystallized from water and dried over sulphuric acid. They melted at 160° . When mixed with the acid melting at 161° , obtained as just described, by the nitration of pyrocoll, they melted at 159° .

The potassium salt was prepared by treating an aqueous solution of potassium carbonate with an excess of the acid, filtering to remove the excess of acid, and concentrating the solution thus obtained by evaporation. It crystallizes in yellow needles without water of crystallization.

α -Nitropyrrole (VII).

0.5 gram of the pure acid melting at 161° was mixed with an equal weight of naphthalene and heated in a sealed tube at a temperature of 175° – 185° for an hour. When the tube was opened a very little pressure was observed. The contents were extracted with hot water from which solution crystals appeared in clusters. These melted at 161° . The pure acid was mixed with naphthalene and heated in a sealed tube, and examined every few minutes. No change other than the melting of the substance was observed when the tube had reached a temperature of 230° . The tube was examined a few moments later when the temperature had risen to 235° , and found to contain a blackened and partly solid mass. The tube was removed and cooled. Considerable pressure was noticeable upon opening. A water extract yielded a small quantity of the original acid. The acid was heated with naphthalene in a sealed tube at 180° – 185° for ten hours. There was pressure in the tube. A water extract of the contents yielded a bright yellow solution which was concentrated on the steam bath and set aside to cool. Small circular or bow-shaped clusters of crystals formed in the bottom of the dish while a bright yellow oil appeared on the sides. The crystals melted at 161° . The oil was removed and set aside in the ice chest. After a week's standing no crystals appeared. This oil had a faint pleasant odor.

α -Carbopyrrolic methyl ester, $C_6H_7O_2N$.

It was necessary to have a considerable quantity of this substance in order to prepare β' -nitro- α -carbopyrrolic acid and α' -nitro- α -carbopyrrolic acid by the nitration method according to Anderlini.¹ These two acids were used to check with those obtained by us by the condensation reaction and by the nitration of pyrocoll.

α -Carbopyrrolic methyl ester was prepared both by the esterification of α -carbopyrrolic acid, and by the method of Oddo.¹

¹ Loc. cit.

The esterification was accomplished as follows: 0.5 gram of carbopyrrolic acid was dissolved in 20 cc. of water and the aqueous solution was made slightly alkaline with barium hydroxide solution. The barium salt thus formed remained in solution. A slight excess of silver nitrate solution was added, whereupon a white, amorphous precipitate formed. This precipitate of the silver salt was filtered at the pump and dried on a porous plate. When completely dry it was placed in a flask fitted with a ground-glass stopper and an equivalent amount of methyl iodide was added. The flask was closed and placed in the steam bath for an hour. After the flask had cooled the contents were extracted with ether. From this extract a deposit of brown crystals was obtained. These were dissolved in ligroin and treated with bone-black in this solution. After evaporation of the solvent there was left a mass of pale red crystals. Repeated crystallization from ligroin failed to rid the substance of the color. The crystals were then placed between large watch glasses which were gently heated on the steam bath. The substance slowly sublimed depositing upon the upper watch glass in the form of beautiful, colorless needles. These crystals melted at 73° . The yield was 60 per cent. of the theoretical. It was found that the substance also crystallized in pure condition from an aqueous solution which had first been treated with bone-black.

In carrying out the method of Oddo, 14.2 grams of dry, freshly distilled methyl iodide were dissolved in dry ether, and this solution was added to 2 grams of magnesium ribbon in dry ether. After the magnesium had completely disappeared, 6.7 grams of dry freshly distilled pyrrole dissolved in ether were added a little at a time. At each addition of pyrrole a gas was evolved, and the reaction was shown to be complete when, upon warming the solution on the steam bath, no more gas was evolved. A green oil separated at the bottom of the flask. To this an equivalent quantity of chlorocarbonic methyl ester dissolved in ether was added a little at a time. A violent reaction ensued. When too great a quantity of the ester was added, the reaction took place in the condenser tube with which the flask was closed, thereby causing the liquid to shoot out at the top of the tube. As the chlorocarbonic ester was added the green oil containing the pyrrole magnesium iodide became yel-

low. The mixture was heated on the steam bath for an hour. The brown oil became very viscous. A large part of the ether was then distilled off, and the contents of the flask were poured into a beaker containing cracked ice. The water formed by the melting of the ice dissolved the viscous oil, and the whole mixture became bright yellow in color. The solution was then made neutral or slightly acidic with acetic acid. It turned brown when acidified. The impure ester was extracted several times with ether and the last traces finally removed by extraction with ethyl acetate. The solvents containing the ester sought were partly evaporated on the steam bath. They were then filtered to remove any resinous material and finally allowed to evaporate spontaneously. There remained a dark brown liquid smelling of pyrrole. This was put away in the ice chest. After several days the substance had completely crystallized. The ester was obtained in the pure form by sublimation as described above. Yield, 2 grams. The ester thus prepared melted at 73° . This method has the advantage that the product sought can be made directly from pyrrole, thus doing away with the somewhat tedious preparation of α -carbopyrrolic acid by heating pyrrole in a sealed tube in the presence of aqueous ammonium carbonate. The ethyl ester was also prepared in good yield by the method of Oddo.

The chlorocarbonic methyl ester used in the above preparation was prepared according to Hentschel's¹ method, by the action of methyl alcohol upon phosgene. The phosgene was prepared as described by Erdmann,² with the exception that we introduced a modification of the apparatus. The phosgene was passed from the reflux condenser of the generating flask directly through an upright coil which was packed in a freezing mixture. The gas condensed in this coil and dropped into a receiving flask also surrounded with ice. When the preparation of the phosgene was finished the apparatus was disconnected, and the dry methyl alcohol poured through the cooling coil into the liquid phosgene. It was found best to add the alcohol very slowly for the reaction was violent, and considerable heat was evolved. Such vapors as were formed, however, were largely condensed when they came into contact with the cold coil. By the use of this apparatus.

¹ Ber. **18**, 1177 (1885).

² Ber. **26**, 1993 (1893).

the ester sought was formed with very little loss of phosgene, in fact only rarely did enough escape to be detected by the odor.

Pyrocoll.

This substance was prepared from gelatine according to the method described by Ciamician.¹ 100 grams of commercial gelatine were placed in a copper retort of about 750 cc. capacity. This retort was of the kind used in the fractional distillation of coal tar. It was fitted with a smooth lid which was held tightly against the retort by a screw clamp. In the lid there was a hole of 18 mm. diameter into which a collar 25 mm. long was tightly screwed. After the gelatine had been pounded down into the retort the lid was fastened on, the retort was clamped on a ring stand at a small angle, and a long, glass condenser tube of 14 mm. diameter was packed tightly into the collar with shredded asbestos. The far end of the condenser tube was led into a receiving flask. The yield of the pyrocoll was found to vary considerably with the manner of heating. The best results were obtained when the heating was fairly rapid and constant. A Meker burner was placed under the upper end of the retort just below the lid, and the full flame was used from the beginning. After the heating had been continued for 10–15 minutes, drops of water condensed in the tube and a brown crystalline substance began to settle on the walls. In 15–20 minutes a yellow or brown oil began to form and to flow down the tube. A white crystalline deposit formed in the receiving flask and at the far end of the tube. This deposit was a mixture of ammonium salts. If the heating was not sufficiently rapid this deposit was found to be the main solid product formed in the distillation. On the other hand, too rapid heating causes the gelatine to foam so that it runs up and chokes the delivery tube. When the brown oil or tar ceased to form, more burners were turned on until the retort became dull red. It was heated in this condition for 5–15 minutes. When the heating had been suspended the tube was removed and placed aside to cool. The distillate in the receiving flask was filtered at the pump by use of a Buchner funnel. There was left on the filter a brown crystalline mass which was washed with alcohol and with water. When the condenser tube had cooled, alcohol was added, the ends of the tube were stoppered and the tube shaken until the tarry material had completely

¹ Loc. cit.

dissolved. The wood alcohol was then poured upon the filter used in filtering the distillate. After filtering, and washing with alcohol and water, the brown or yellow deposit was removed and dried on a porous plate. Yield of the crude product, 0.4–0.6 gram. The yield was found to vary considerably also with the quality of the gelatine used. The best quality obtainable failed to yield so well as the somewhat yellower inferior brands. The yield from commercial glue was much smaller than from gelatine. The crude pyrocoll was purified by recrystallization from boiling glacial acetic acid. It melted at 268° .

SUMMARY.

In this investigation it is shown that nitromalonic aldehyde and glycine ester can be brought into condensation to form first an open chain compound and eventually a nitro derivative of pyrrole. The final product is a nitropyrrole- α -carboxylic acid. The position of the nitro group in the ring is fixed by reason of the relationship existing in the chain compound from which the product is formed. With this position of the nitro group thus determined the constitution of the corresponding nitropyrrole itself becomes known, and consequently by processes of exclusion the corresponding constitutions of the two remaining nitropyrrole- α -carboxylic acids are open for interpretation. It is shown that one of these latter acids, in common with the acid of known structure, has the property of losing carbon dioxide when heated, thus forming a new dimolecular nitropyrrole, whereas the third acid forms in the same manner a different nitropyrrole. These facts at once reveal the structures of the three acids. The relationship existing between various nitropyrroles is also established.



